REMARKS

The presently claimed invention features fohy030 and fomy030 polypeptides. Fohy030 and fomy030 are expressed at a much lower level melanoma cells having relatively high metastatic potential than in melanoma cells having relatively low metastatic potential. Accordingly, fohy030 and fomy030 polypeptides and nucleic acids are useful in the diagnosis and monitoring of melanoma.

The non-elected claims have been cancelled. The pending claims have been reiterated for the Examiner's convenience.

Rejections Under 35 U.S.C. §101

The Examiner rejected claims 29, 31-38, 43 and 45-56 under 35 U.S.C. §101 as allegedly lacking utility. Applicant traverses the rejection of claims 29, 31-38, 43 and 45-56.

According to the Examiner, claims 29, 31-38, 43 and 45-56 lack utility because "the specification does not teach that changes in the levels of polynucleotide sequences of SEQ ID NO:2, 6 and 8 correlate with changes in the levels of the corresponding encoded proteins, wherein said protein levels would be indicative of a disease state." In support of this assertion, the Examiner cited a number of publications said to describe genes that are subject to control at the translational level (McClean et al.; Shantz et al.; and Fu et al.)

The cited publications do not provide any basis for concluding that the fohy030 gene and the fomy030 gene are subject to translational control

As explained previously, the genes described in each of the publications cited by the Examiner include specific structural elements or other factors that appear to be required for translational control. For example, Shantz et al. identify at least three structural features of ODC mRNA that are likely to be responsible for translational regulation: 5' UTR in the mRNA that can adopt a specific secondary structure that might be melted by certain translation factors, an internal ORF, and a potential polyamine responsive element in the 5' UTR. Shantz et al. report that translational regulation of the AdoMetDC gene might be due to a small ORF in the 5'UTR of the mRNA and a polyamine response element in the 5' UTR of the mRNA. Fu et al. report that translational control of p53 observed in some cell types may be due to the presence of a specific sequence in the 3' UTR of the mRNA.

Each gene studied in the cited publications includes special structural elements are responsible for the observed translational regulation. The Examiner has not provided any evidence suggesting that any of these specialized elements are present in the fohy030 and fomy030 genes. The Examiner has not even pointed to any reason to think that fohy030 is similar in its regulation to any of the genes cited in the publications. Thus, the Examiner has failed to provide any basis for the assertion that the foh030 gene is under translational control.

"The PTO has the initial burden of chailenging a patent applicant's presumptively correct assertion of utility. ...If the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility, however, the burden shifts to the applicant to submit evidence sufficient to convince such a person of the invention's asserted utility." *In re Swartz*, 232 F.3d 862, 866 (Fed. Cir. 2000). The Examiner has not met his burden of providing evidence or reasoning that would cause one of ordinary skill to doubt the utility of the presently claimed invention. Thus, the rejection is not warranted. Moreover, as explained below, there is ample basis for concluding that fohy030 protein expression has the same pattern as fohy030 polypeptide expression.

The expression pattern of fohy030 mRNA in clinical samples makes it reasonable to assume that fogy030 protein follows a similar expression pattern

There is ample evidence—including evidence from clinical samples—that fohy030 mRNA expression is reduced in melanoma. Based on this consistent expression patter, it is reasonable to assume that fohy030 protein expression follows a similar pattern.

As the specification explains (page 125), the expression of fohy030 in clinical samples of melanoma cells is higher in non-metastatic melanocytes from benign nevi and in normal melaoncytes than in metastatic melonocytes. A recent publication reporting on the analysis of a larger number of clinical samples revealed a similar correlation (*Human Pathol.* (2000) 31(11):1346-56; copy attached). This publication reports on a detailed examination of the histological patterns of melastatin (fohy030) mRNA expression in nevi, primary melanoma, and melanoma metastases. The authors found ubiquitous melanocytic expression of melastatin mRNA was observed in all benign melanocytic proliferations (14 of 14) with some nevi showed a gradient of reduced melastatin expression with increased dermal depth (3 of 14). In addition, uniform expression of melastatin mRNA was observed in 49% of primary cutaneous melanomas

(18 of 37 cases, including 1 case of *in situ* melanoma). Melastatin mRNA loss by a portion of the melanoma was identified in 53% of the invasive melanoma samples (19 of 36) and 100% of the melanoma metastases (11 of 11). Moreover, within the invasive melanoma samples, melastatin loss was correlated with tumor thickness. Thus, primary melanomas without melastatin mRNA loss ranged in thickness from 0.17 to 2.75 mm (median, 0.5 mm; mean, 0.73 mm). In contrast, whereas primary melanomas that expressed melastatin mRNA loss ranged in thickness from 0.28 to 5.75 mm (median, 1.7 mm; mean, 2.13 mm). Of the 11 melanoma metastases examined, 64% displayed focal melastatin mRNA loss, and 36% had complete loss of melastatin mRNA expression. Thus, the clinical sample examined showed a striking correlation between low or no melastatin mRNA expression and conversion to a metastatic state.

Given the striking and consistent correlation between fohy030 mRNA expression and metastatic state, as demonstrated in the specification and confirmed in a subsequent publication, it is reasonable to assume that fohy030 protein expression follows a similar pattern. Accordingly, one skilled in the art would conclude that the claimed polypeptides have utility. In view of the forgoing, Applicants respectfully request that the rejections under 35 U.S.C. §101 be withdrawn

Rejections Under 35 U.S.C. §112, first paragraph (written description)

The Examiner rejected claims 37, 38, 43 and 45-56 under 35 U.S.C. §112, first paragraph as allegedly not supported by an adequate written description.

The Examiner stated that Applicant's earlier submitted arguments for regarding the adequacy of the written description supporting claims 37, 38 and 45-56 was not persuasive because "the specification did not provide any objective evidence that applicant had the variant polypeptide in hand at the time the instant application was filed." Applicants request that the Examiner clarify the requirement that the specification provide "objection evidence" that "applicant had the variant polypeptide in hand." The Examiner's reference to "objective evidence" suggests that the Examiner is requiring evidence that Applicant had actually reduced the claimed polypeptides to practice at the time the application was filed and thus had actual physical possession of the claimed polypeptides. Applicants do not believe that the relevant case law imposes such are requirement. As explained in greater detail below, The specification

provides an adequate written description of the claimed polypeptides by virtue of providing a description of their structure and/or physical properties.

Claims 37 and 38

In rejecting claims 37 and 38 the Examiner stated that there "are no examples in the in the specification of a genus of polypeptides comprising amino acids 1-844 of SEQ ID NO:7 or a genus of polypeptides comprising amino acids 850-1497 of SEQ ID NO:7." Applicant believes that the Examiner is asserting that the specification does not provide an adequate number of species that fall within each genus. Applicant disagrees. The specification discloses polypeptides comprising amino acids 1-844, 1-845, 1-846, 1-847, etc of SEQ ID NO:7. All of these polypeptides are within the genus of claim 37. Similarly, the specification discloses polypeptides comprising amino acids 1-1497, 2-1497, 3-1497, etc. of SEQ ID NO:7. All of these polypeptides are within the genus of claim 38. Thus, the specification clearly discloses numerous species within the genus of each claim.

Regents of the University of California v. Lilly & Co., 119 F.3d 1559, 1563 (Fed. Cir. 1997), emphasizes that an appropriate written description of a cDNA "requires a precise definition, such as by structure, formula, chemical name, or physical characteristics." *Lilly* holds that a proper written description of a genus of cDNAs can be achieved in two alternative ways: "by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within in the scope of the genus **or** of **a recitation of structural features common to members of the genus**." *Lilly*, 119 F.3d at 1563 (emphasis added). Claims 37 and 38 are drawn to polypeptides comprising specified amino acids of SEQ ID NO:7. To the extent that claims 37 and 38 are genus claims, the specified portion of SEQ ID NO:7 amounts to a description of a structural feature common to members of the genus. Thus, claims 37 and 38 clearly meet the written description requirement.

Claims 43 and 45-56

Claims 43 and 45-56 are drawn to drawn to polypeptides that are encoded by a nucleic acid molecule that hybridizes under defined conditions to a nucleic acid molecule consisting of the nucleotide sequence of a specified fohy030 or fomy030 cDNA and which when expressed in a melanoma cell is associated with decreased metastatic potential of the melanoma cell compared to an otherwise identical melanoma cell that does not express the polypeptide. Thus, the

polypeptides are defined via the nucleic acid molecules encoding them. This amounts to a structural definition based on the sequence of the polypeptide, which sequence is defined by the sequence of the hybridizing nucleic acid molecule that encode the polypeptide. The claims also include a functional limitation since the polypeptide, when expressed in a melanoma cell is associated with decreased metastatic potential.

The Examiner appears to find that the claims do not meet the written description requirement because, according to the Examiner, "there are no examples in the specification of a genus of polypeptides obtained by the claimed hybridization methods, or a description of the necessary chemical features that must be part of the claimed genus." However, as explained above, the present claims include both structural and functional limitations. Thus, it is Applicant's position that the written description requirement has been fully met for claims 43 and 45-56.

In view of the forgoing, Applicants respectfully request that the rejection of claims 27, 28 and 45-56 under the written description requirement of 35 U.S.C. §112, first paragraph be withdrawn.

Conclusion

Applicant asks that all claims be allowed. Enclosed is a check for the Petition for Extension of Time fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 7 MAY 2002

Anita L. Meiklejohn, Ph.D.
Reg. No. 35,283

Fish & Richardson P.C.
225 Franklin Street
Boston, Massachusetts 02110-2804
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

20430034.doc